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Cardiopulmonary bypass associated acute kidney injury: better understanding and better prevention

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ABSTRACT

Cardiopulmonary bypass (CPB) is a common technique in cardiac surgery but is associated with acute kidney injury (AKI), which carries considerable morbidity and mortality. In this review, we explore the range and definition of CPB-associated AKI and discuss the possible impact of different disease recognition methods on research outcomes. Furthermore, we introduce the specialized equipment and procedural intricacies associated with CPB surgeries. Based on recent research, we discuss the potential pathogenesis of AKI that may result from CPB, including compromised perfusion and oxygenation, inflammatory activation, oxidative stress, coagulopathy, hemolysis, and endothelial damage. Finally, we explore current interventions aimed at preventing and attenuating renal impairment related to CPB, and presenting these measures from three perspectives: (1) avoiding CPB to eliminate the fundamental impact on renal function; (2) optimizing CPB by adjusting equipment parameters, optimizing surgical procedures, or using improved materials to mitigate kidney damage; (3) employing pharmacological or interventional measures targeting pathogenic factors.

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Introduction

Acute kidney injury (AKI) is a common and severe complication after cardiac surgery, and there are more than 2 million cardiac surgeries performed worldwide each year [1]. The incidence of AKI varies from 1 to 40% due to differences in study populations and disease definitions [2–4], but regardless, even mildly elevated serum creatinine is associated with poor prognosis and increased mortality [5].

Clinical classification plays a prominent role in distinguishing diseases [6]. An explicit diagnosis is indispensable for pathology analysis and enables doctors to communicate with peers, explore the illness, and cure the patient. Although cardiorenal syndrome (CRS) provides a solid theoretical framework, there is no consensus about the definition of cardiac surgery-associated AKI (CSA-AKI); many previous studies might use the Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE) or the AKI Network (AKIN) criteria or even customizable standards to define CSA-AKI, which could partially contribute to the discrepancy in results [7–9].

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines redefined AKI, which was then used to diagnose CSA-AKI and revealed noninferiority compared with the RIFLE and AKIN classifications [10]. Later, a large multicenter cohort study demonstrated the prognostic effectiveness of the KDIGO definition at any AKI stage after cardiac surgery [11], and this KDIGO definition is increasingly used in classifying CSA-AKI [12]. Any patient who has had cardiac surgery in the past week and who fulfills the KDIGO criteria for AKI can be said to have CSA-AKI [13]. As a devastating disease, CSA-AKI not only is an immediately difficult complication but also has severe consequences, with some suggesting that the composite outcome of CSA-AKI includes death, new dialysis requirements, and worsened renal function (a 25% or greater reduction in the eGFR). The major adverse kidney event (MAKE) may be a suitable endpoint for study [14], especially since nephrologists assess the progression of chronic kidney disease (CKD) 90 days later.

The serum creatinine concentration is a poor indicator of renal dysfunction [15], and urine output can be easily influenced during the perioperative period. The clinical diagnosis of CSA-AKI relies on traits intrinsic to AKI, the last stage of the four-phase nephron theory, which indicates kidney damage and loss of function [16]. All of the above factors contribute to delayed diagnosis and limited

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therapeutic efficacy; therefore, sensitive and effective biomarkers for the early prediction of CSA-AKI have always been a research focus; fortunately, several of these biomarkers have demonstrated the ability to detect renal injury and are likely to be applied in future clinical practice [17–19]. However, researches about biomarkers are out of scope in this review.

Cardiac surgery consists of a series of operations that primarily involve the cardiovascular tract and valves; since the first cardiopulmonary bypass (CPB) procedure was successfully conducted in 1953 [20], surgeries on nonbeating hearts have become mainstream procedures in a short period of time. However, exposure to an artificial bypass surface, nonpulsatile flow, cross-clamping of the aorta, a higher dose of heparin, and hypothermia [21,22] are related to the inflammatory response, laminar flow, cold cardiac ischemia, coagulation, and activation of platelets and leukocytes [23] and could result in consequential acute renal failure. With the development of surgical techniques, coronary artery bypass grafting (CABG) without CPB (off-pump CABG, or OPCAB) is becoming more sophisticated, and controversies between proponents of on-pump and proponents of off-pump ensue. Several investigations have indicated that CPB directly damages the kidney and is independently associated with postoperative AKI [22, 24–26], while others have reported no additional adverse renal events when compared with those in the off-pump group [27–30]. However, most of these studies focused on the first 30 days and dialysis-required renal failure instead of the impairment of the kidney. Furthermore, there is no formal categorization of CPB and non-CPB procedures in the context of CSA-AKI, and some studies fail to provide explicit descriptions of CPB conditions among cardiac surgery populations. In summary, there are still many issues to be clarified about CSA-AKI, and in this review, we mainly discuss the unique role and pathological mechanisms of CPB in the clinical course of AKI and propose targeted preventive measures for CPB-associated AKI based on recent studies.

Cardiopulmonary bypass

The purposes of extracorporeal circulation is to provide a bloodless area within the cardiac chambers [31] and also stop the beating heart to facilitate definitive surgery. Unlike usual surgical procedures, CPB involves cardiac arrest, blood suction device, nonbiological surface circuits, pumps, altered pulsatile blood flow, extracorporeal oxygenation, activation of inflammation, anticoagulation, and the external thermoregulation, which induces a series of physiological and pathological changes. In addition, compared with non-CPB surgery, CPB requires excellent coordination among surgeons, perfusionists, and anesthesiologists and exhibits a more pronounced correlation between the volume of surgeries in medical institution and surgical outcomes [32]. The following table provides a brief comparison of on-pump and off-pump procedures, which helps to distinguish the unique factors of CPB (Table 1).

Table 1. On-pump surgery versus off-pump surgery [33–36].

	ON-PUMP	OFF-PUMP
PUMP	YES	NO
PERFUSION	YES	NO
HEMOLYSIS	YES	NO†
NON-BIOLOGICAL SURFACES CIRCUIT	YES	NO
AORTIC CROSS-CLAMPING	YES (ABOUT 1H)	NO
CARDIAC ARREST	YES	NO
HEPARIN	HIGHER DOSE*	LOWER DOSE MOSTLY**
PROTAMINE	YES	OCCASIONALLY
HYPOTHERMIA	YES	NO
MICROEMBOLI	YES	NO†
NEGATIVE PRESSURE OF SUCTION	YES	NO
HAEMODILUTION	YES	NO
CONTRAST AGENT	NO	YES

†No conclusive evidence available.
*Target activated clotting time (ACT) more than 480s.
**The majority dose of heparin < 300 IU/kg.

Pathology mechanism

Hypoperfusion and hypoxia

How to balance the blood flow of the pump has always been a difficult decision in extracorporeal circulation. Guyton explained the infinite feedback gain property of the renal fluid mechanism: theoretically, prior to functional change, the kidney can sustain the stabilization of arterial pressure by regulating urine output [37]. However, it seems that cardiac arrest terminates this circulatory mechanism. During the CPB process, systemic blood pressure and renal blood flow are closely correlated with pump flow [38,39], which means that low flow will directly lead to inadequate organ perfusion. In contrast, the load caused by high flow rates, as well as fluid resuscitation therapy, can cause sodium retention problems.

Water-sodium retention caused by heart failure or fluid resuscitation is common during cardiac surgery with CPB; thus, central venous pressure (CVP) is easily influenced, and a notable increase in renal venous pressure could significantly affect peritubular capillary blood flow and the glomerular ultrafiltration gradient [40,41]. In turn, impaired kidney function following hypoperfusion aggravates liquid retention, yielding a vicious cycle. Researchers have demonstrated that a high CVP is independently associated with AKI after cardiac surgery with CPB [42–44], and portal flow pulsatility and intrarenal flow patterns are good predictive indicators [42]; more importantly, compared with measuring CVP, these ultrasound features are noninvasive and can be assessed at the bedside rapidly and repeatedly. In addition, a high CVP hampers venous return and increases capillary hydrostatic pressure, which could promote renal interstitium oedema [41].

Hypoxia ensues due to inadequate renal perfusion. The oxygen tissue partial pressure of the kidney outer medulla is widely acknowledged to be 10–20 mmHg under normal conditions, one-fifth of that of the cortex [45], increasing sensitivity to hypoxia and increasing vulnerability during surgery. The application of CPB in particular exacerbates this situation; both mathematical [46,47] and animal [48,49] models have illustrated this point.

Kidney oxygen utilization mainly consists of sodium resorption and basal oxygen consumption, and renal oxygenation can be described as the extraction of O_2 (O_2Ex), which is equal to the ratio of renal oxygen consumption (RVO_2) to renal oxygen delivery (RDO_2), and elevated O_2Ex levels suggest kidney impairment. Under normal conditions, O_2Ex can remain stable during a wide range of kidney blood flow changes by regulating oxygen consumption through sodium reabsorption and the glomerular filtration rate (GFR) [45]. According to this theory, a decrease in the GFR in AKI patients could minimize the workload of tubular reabsorption and prevent further aggravation of ischemia; however, after the CBP procedure, the RVO_2 was not proportionally reduced compared with the GFR and sodium resorption in the AKI and non-AKI groups [50], which indicates that additional factors might be involved in the increase in RVO_2 among AKI patients; a similar result can be found in ischemic rat models [51]. During CPB, even with a certain pump flow rate and no significant difference in renal perfusion, compared with pre-CPB, DVO_2 decreases markedly, while RVO_2 and sodium reabsorption change inconspicuously, possibly through the redistribution of kidney blood flow and haemodilution [52]. All the above findings imply that complications are not confined to the extracorporeal flow period but also compensatory function impairment after weaning from CPB.

Inflammation

The Chenoweth team was the first to confirm complement activation during extracorporeal procedures [53], and the understanding of the inflammatory reactions associated with CPB has improved with the discovery of inflammatory mediators [54,55]. During the progression of CPB, contact with nonendothelialized surfaces of the extracorporeal circuit could activate an alternate complement pathway in addition to triggering factor XII. Factor XII could generate inflammatory mediators, such as bradykinin, which are involved in coagulation dysfunction, and further products could trigger the classical complement pathway; moreover, the loss of pulsatile blood flow is also associated with the activation of inflammation [53, 56–58]. Additionally, to reverse the function of heparin at the end of CPB, the administration of protamine is necessary, but research shows that protamine-heparin complexes could aggravate the inflammatory response [59,60].

Interleukin (IL)-6 is a critical cytokine in AKI that has both proinflammatory and anti-inflammatory effects [61], and an ischemic mouse model validates the compensatory anti-inflammatory response effect of IL-10, which predominantly occurs in the spleen and is regulated by IL-6 [62]. In a large-scale cardiac surgery population that underwent CPB, the perioperative levels of serum IL-6 and IL-10 were elevated, particularly in the AKI group, and the temporal profiles of the two biomarkers confirmed previous findings [63]. In addition to inflammatory factors, the coagulation cascade, endothelial cell damage and platelet activation [64] also involve systematic responses and might be involved in the early and late phases [65]. Many novel inflammatory biomarkers, such as CXC chemokine ligands and endothelin, are elevated after pediatric heart surgery [66], and currently, tissue hormones, such as subfatin, maresin-1, asprosin, and alamandine, were first discovered to be related to CPB and might be prospective therapeutic targets [67].

The proinflammatory role of CPB has been demonstrated in multiple studies, which revealed a positive correlation between CPB and aortic cross-clamping time [68,69]. During surgery and the early postoperative period, the peak level of proinflammatory mediators is significantly greater in patients with CPB than in patients without CPB, and the difference in inflammatory status subsides and eventually offsets during the ensuing postoperative period [70]. However, when CPB is avoided, there is evidence that inflammation still occurs, with a slight delay compared to extracorporeal circulation [57].

New multi-gene expression analysis approaches such as the microarray technique [71] overcomes the limitations of single-gene approaches in assessing complex pathophysiological networks, and investigators have shown that CPB triggers a short-lasting inflammatory reaction; cytokines; and chemokines, such as IL-8, IL-10, and monocyte chemoattractant protein-1 (MCP-1); moreover, macrophage inflammatory protein 1β (MIP-1β) is indeed associated with the initiation of CPB. Although some proinflammatory gene products are induced to a similar extent during off-pump surgery, the time course of induction is strikingly different [34]. However, limited by the surgical procedure itself, even though the baseline conditions of both groups were comparable, more coronary artery disease-affected vessels and more prolonged mechanical ventilation time were observed in the on-pump group.

In addition to the CPB-associated systemic inflammatory response syndrome, the postoperative anti-inflammatory response has also been a research hotspot in recent years. Immunoparalysis represents impaired immune defence, which is regarded as the outcome of an exaggerated or prolonged anti-inflammatory response after CPB and is considered relevant to the IL-10 genotype [72,73], and peroxiredoxin-1, a cytosolic antioxidant released during CPB, can induce phagocytes to produce IL-10 *via* Toll-like receptor (TLR) 4 [74]. The latest study showed that increased monocytic myeloid-derived suppressor cells and insufficient L-arginine might also be responsible for postoperative immunoparalysis [75], and cell population data, consisting of leukocyte size, granularity, and fluorescence intensity, are strongly associated with CPB and might be suitable for monitoring the activation of immunity [76].

Interestingly, the piglet model revealed the correlation between CPB and the derangement of the intestinal microbiome, which might account for systematic inflammation [77] and provide us with a new direction for treatment.

Oxidative stress

Reactive oxygen species (ROS) can increase abnormally under hypoxia and reperfusion conditions and lead to the

modification of lipids (especially arachidonic acid), proteins (including nitration, chlorination, and bromination, all of which are associated with inflammation), and deoxyribonucleic acid (DNA), which causes variations in protein expression [78]. To eliminate the disturbance of varying oxygen concentrations during CPB, a clinical trial measured two kinds of oxidative stress indicators, F2-isoprostanes and isofurans, and confirmed oxidative damage in both peripheral tissues and the kidney itself, which might be attributed to hemolysis and rhabdomyolysis [79]. In addition to the end products of arachidonic acid, lipid peroxidation generates assorted metabolites; recently, malondialdehyde has been demonstrated to be a promising biomarker of oxidative stress and remains high after two days of CPB [80]. The nonenzymatic antioxidants vitamin C and vitamin E also decrease sharply and remain low postoperatively [81], but the blood concentration of glutathione (GSH) shows a progressive increase and reaches culmination at the end of CPB [82], which might indicate a compensatory mechanism. As a promoter of fatty acid metabolism, peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is decreased in diabetic patients undergoing CPB and impedes mitochondrial function and leads to oxidative injury in cardiac tissue [83], while PGC-1α does not change significantly in another mixed group with an approximate 50% incidence of diabetes. Investigators have shown that mitochondrial DNA damage and mitophagy occur during CPB through biopsy experiments of the right atrial appendage [84]. However, these pathological processes in the kidney still need to be described in the future.

Iron metabolism is essential for oxidative stress and induces assorted damage to the tubular epithelium. There is growing evidence that iron metabolism plays an important role in CPB-related AKI and is regarded as a form of renal sideropathy [85]. Owing to haemodilution and exposure to the nonbiological surface during CPB, chelatable iron can be released from extracorporeally circulated blood [86], which might induce iron deficiency. However, recently, a small sample study revealed no difference in the serum iron concentration between AKI patients and non-AKI patients despite the transient decreasing trend; in contrast, the levels of copper, zinc, and selenium decreased markedly within a short time after CPB in AKI patients and are likely to interfere with the capacity against oxidative stress [87]. A retrospective study of the nonanaemia population suggested that the incidence of postoperative AKI is not significantly affected by iron deficiency [88]. Although intravenous treatment of ferric carboxymaltose within 2 days before cardiac surgery results in iron storage in anemic patients [89], the renoprotective role of maintaining iron homeostasis in CPB patients still needs to be clarified.

Metabolomic research on animals has shown that both tryptophan and purine metabolism are influenced during CPB and that the level of metabolites changes significantly in AKI patients [90], which is consistent with clinical observations [91,92]; however, less is known about the pathogenic process involved. The antioxidant system of preterm infants is immature [93], and these infants are exposed to more severe oxidative stress during CPB than is currently known [94]; thus, consideration of age is indispensable when developing preventive therapies.

Coagulation and hemolysis

As mentioned above, CPB involves extracorporeal piping, which can lead to activation of the coagulation pathway when blood cells contact the artificial material [95–97]. Although the generation of thrombin was also observed in OPCAB patients, it occurred later and more gradually than in CPB patients and without platelet activation [98]; however, these results differ from those of another study in which tranexamic acid was used perioperatively [99]. Surprisingly, a recent study revealed that a high level of the thrombin–antithrombin complex is related to AKI after CPB in a group of toddler patients but not in infants [100]. Moreover, CPB can cause platelet dysfunction and increased haemorrhage [101], resulting in a growing demand for blood transfusions [102].

The fibrinolytic system is activated during the initial period of CPB, accompanied by a notable increase in tissue-type plasminogen activator [99, 103]; however, the antithrombotic effect is soon offset by the release of plasminogen activator inhibitor-1 (PAI-1), which can be promoted through angiotensin II [103], and PAI has recently been shown to participate in acute lung injury after CPB by inducing endothelial cell-derived extracellular vesicles [104]. Thus, angiotensin-converting enzyme inhibitors (ACEis) might reduce PAI-1 levels and alleviate organ injury, but considering the increase in bradykinin, a stimulator of IL-6 expression [105], the comprehensive role of ACEis in cardiac surgery patients still needs to be clarified. Furthermore, macro- and microembolism gases and particulates are frequently generated during CPB [106] and aggravate coagulation disorders.

Hemolysis can also be attributed to CPB, as the turbulence, cavitation, and osmotic stresses during CPB result in red blood cell membrane injury and haemolysis [107]; moreover, negative pressure applied during CPB suction of blood and contact with the air surface could also induce and exacerbate haemolysis [108,109]. The level of free hemoglobin (Hb), a product of erythrocyte destruction, is markedly elevated in patients undergoing on-pump surgery compared with patients undergoing OPCAB [110], and free Hb is associated with increased consumption of nitric oxide (NO) and aggravated intrarenal oxidative reactions [111].

To reduce the risk of bleeding and blood cell transfusion, tranexamic acid is often administered during CPB, but there is no consensus on the optimal dosage [112]; recently, a large-scale randomized trial verified that no obvious difference exists between high and low doses of tranexamic acid in hemostatic effects and renal dysfunction [113].

Others

Endothelial cells regulate vasopermeability, vascular tension, inflammatory, and coagulation responses, and structural or functional breakdown can lead to AKI [114]. Growing

evidence suggests that the endothelial structure is destroyed during cardiac surgery, and ANP is the most likely initiating mediator [115–117]; moreover, the serum levels of glycocalyx components (syndecan-1 and hyaluronan) were greater in the CPB group than in the OPCAB group, indicating that more severe endothelial damage existed in the extracorporeal cycle [116]. Recent investigations have suggested that endothelial dysfunction might cause hyperpermeability to impair microcirculatory perfusion [118]; therefore, successful endothelial protection could be treated as renal protection, and an animal model revealed the endothelial protective effect of imatinib and moderated fluid leakage and subsequent kidney damage [119], despite the use of the beating-heart CPB model.

Particulate, gaseous, and lipid microemboli (LMEs) are side effects of CPB surgery, and manual manipulation of the cardiovascular region and the components of the extracorporeal circuit are the primary sources of microemboli [120–122]. These effects might lead to endothelial dysfunction and vascular blockage [123] and decrease the quality of blood flow and capillary oxygen delivery [124].

In animal studies, elevated levels of LME were found in the kidney after the CPB procedure and induced renal damage [120]; in a subsequent cardiac surgery patient cohort, filtration of LME was considered renoprotective [125]. Some optimization strategies for surgical methods (such as minimally invasive extracorporeal circulation (MiECC) [126] and hematic antegrade repriming127] and modified devices [124] are both effective at reducing microemboli.

However, current studies have focused mainly on postoperative neurocognitive disorders, and the impact of CPB-related microemboli activity on the kidney has yet to be determined.

Prevention

Avert CPB

Valvular heart disease

The field of minimally invasive interventional treatment for structural heart disease is rapidly advancing, with an increasing number of heart valve interventions each year. Techniques such as transcatheter aortic valve replacement (TAVR) [128] and transcatheter edge-to-edge repair (TEER) [129] are increasingly recommended for patients with an expected lifespan of more than one year who are at high surgical risk due to advanced age. Although these approaches fundamentally eliminate the impact of CPB, they require precise anatomical suitability and carry the potential for requiring unplanned extracorporeal circulation support.

Macroangiopathy

Intraluminal techniques are also being applied in major vascular surgeries [130], such as hybrid aortic arch repair (HAR) and endovascular aortic arch repair (EAR), to effectively avoid circulatory arrest and cross-clamping; these techniques have become minimally invasive surgical options for treating complex aortic arch diseases and are particularly suitable for patients at greater surgical risk. However, current research has not yet confirmed the clinical efficacy of these methods compared with open surgery [131,132]. Additionally, morphologic suitability remains the most crucial criterion in deciding between endovascular and open surgical treatments [133].

Coronary artery disease

With the improvements in methods for coronary artery stabilization and exposure, beating heart surgery, such as OPCAB, has attracted increased interest [107], but the benefits and risks of an off-pump versus on-pump approach have been debated. Patients in certain patient subgroups, including older patients, females, those with a history of stroke, renal impairment, and pulmonary disease, are considered to benefit more from OPCAB surgery than are other patients [134]. Numerous studies have confirmed the effectiveness of off-pump surgery compared to on-pump surgery in reducing postoperative renal dysfunction [30, 135–137], and renal function might be a factor influencing the choice of revascularization strategy. However, there were no significant differences in long-term renal outcomes [135,136].

In addition, some studies have shown that, compared with patients who underwent CPB, patients who underwent OPCAB had a greater risk of recurrent angina and revascularization within the first postoperative year, as well as 3-year all-cause mortality [138]. However, there was no significant difference in the incidence of renal failure between the two groups. Interestingly, in the ROOBY trial, there was no difference in the incidence of short-term renal failure requiring dialysis, whereas at the one- and five-year follow-ups [28, 139], all-cause mortality was found to be greater in the on-pump CABG group. When the follow-up period extended to ten years, no significant difference in terms of death or revascularization was observed [140]; thus, in the absence of contraindications, CPB could not be replaced yet.

In summary, the decision to apply CPB is primarily determined by the suitability of the disease and surgery. Interventional treatments are recommended for populations at advanced age, long expected lifespan, and high surgical risk. Whether patients at high risk for AKI should be included in the indications for interventional treatment requires further exploration. Additionally, the importance of long-term follow-up outcomes should not be overlooked.

Optimized CPB

Flow rate

Based on clinical guidelines, the target blood flow during CPB depends on the body surface area and temperature and is usually 2.2 to 2.8 L/min/m2 under nondeep hypothermia conditions [141]. However, there has always been debate regarding the optimal setting of flow rates.

The aforementioned discussion established a correlation between DO2 and postoperative AKI outcomes. Since DO2 during CPB is a modifiable factor, achievable through

adjusting pump flow rates, goal-directed perfusion management (GDP) is a theoretically viable approach [142]. Investigators confirmed that maintenance of oxygen delivery over 300 mL O2/min/m2 driven by a higher pump flow rate contributed to a lower incidence of AKI than that of matched historical patient records according to their algorithm [143], while the threshold might be greater in neonates due to an increased metabolic rate [144]. Later, a randomized controlled trial also indicated that a higher flow rate can improve renal O2Ex [145], although only ten minutes of observation and no renal blood flow (RBF) measurements were performed. While these findings are promising, mastering the extracorporeal pump requires strictly skilled perfusionists, and large-scale experimental validation is indispensable. Further investigations are needed to clarify the relationship between perfusion and renal oxygen during the CPB period.

Retrospective studies have shown that mini-CPB was associated with a decreased risk of AKI [146,147], and although the mean cardiopulmonary bypass pump flow was significantly lower with mini-CPB, less haemodilution compensated for this reduction and resulted in a similar calculated DO2 compared with that of normal CPB. However, the causal relationship between mini-CPB and AKI events could not be assessed by retrospective analysis alone. Randomized trials are needed to determine the clinical benefit of these treatments because the majority of patients in clinical trials had normal renal function. The benefit of related initiatives in patients with preoperative renal insufficiency still needs to be investigated [143].

Haemodilution

A lower hematocrit is thought to be correlated with better microcirculation during CPB, but currently, evidence suggests that haemodilution is more likely to result in adverse outcomes, including renal failure [148,149].

Retrograde autologous priming (RAP) is a strategy used to limit haemodilution and transfusion requirements and has been found to be effective in clinical trials [150]. In a small-size study, the combination of low-prime perfusion and autologous prime perfusion reduced the incidence of low hematocrit (<20%) and promoted kidney outcomes [151]. However, the benefit for renal function could not be confirmed in the present study [152,153] or in the meta-analysis [154].

Red blood cell transfusion can also alleviate haemodilution but is strongly associated with ischemic postoperative morbidity in patients undergoing cardiac surgery [155]. However, both a high-quality randomized controlled trial (RCT) [156] and a meta-analysis [157] demonstrated that there was no significant difference between the restrictive transfusion strategy and the liberal strategy in terms of morbidity due to postoperative AKI. In addition, we found that transfusion practices varied due to the absence of a uniform indication of hematocrit for blood transfusion, which may have resulted in heterogeneity among the studies.

Biocompatibility

Attempts have been made to apply diverse materials for surface coating of circuit components, aiming to improve biocompatibility and substantially reduce inflammation and thrombogenesis.

Heparin-bonded circuits, which utilize covalent bonding, have been shown to reduce inflammation and platelet activation, thereby decreasing bleeding and the need for transfusions [158,159]. Some newer coatings, including biocompatible ions, poly-2-methoxyethylacrylate, phosphorylcholine, and trillium, have also shown satisfactory and similar results, and the clinical benefits of one type of coating over another remain controversial [160,161].

The efficacy of biocompatible CPB circuits in alleviating postoperative renal damage is still a subject of debate [162]. Additionally, it remains uncertain whether these observed differences are attributable to design variables or the specific types of coatings employed. Moreover, the integral effects of material-independent blood activation (blood–air interface, cardiotomy suction, hemolysis, etc.) may eventually blunt the total effect of biocompatible surfaces [163].

Recently, the fully magnetically levitated, continuous-flow blood pump in the left ventricular assist system has been shown to enhance haemocompatibility and reduce shear stress on blood components [164] and is hopefully applied in CPB surgery to reduce intraprocedural hemolysis.

Pump

The roller pump and centrifugal pump are two types of CPB pump with different physical designs and physiological effects [33], and in an RCT meta-analysis, there were no significant differences in haematological variables, postoperative blood loss, blood transfusion, neurological outcomes, or mortality between the two pump types [165].

According to the results of single-centre experiments, roller pumps are more prone to thrombotic complications because of the increased aggregation of platelets [166], and centrifugal pumps might reduce the generation of tissue factors [167] and the inflammatory response [168].

Guidelines recommend considering the use of centrifugal pumps for longer durations of anticipated CPB. Although clinical data about renal outcomes are still lacking, centrifugal pumps are theoretically more protective for the kidney than are other methods, considering the potential pathological mechanisms involved.

Perfusion pulsation

The advantage of pulsatile over nonpulsatile perfusion is widely discussed among perfusionists. Pulsatile flow is considered more physiological because it imitates the arterial pulse generated by the heart and is becoming the preferred perfusion method for CPB [169,170].

A meta-analysis suggested that pulsatile perfusion during CPB is beneficial for renal preservation [171]; moreover, pulsatile flow might also reduce inflammatory cytokines and alleviate endothelial damage [172] and has better

biocompatibility than extracorporeal circulation according to scanning electron microscopy (SEM) [173].

However, in a recent prospective observational study, pulsatile flow resulted in a greater extent of hemolysis during the CPB procedure, which is likely attributed to higher circuit pressures and shear forces than nonpulsatile flow [174].

It should be emphasized that the inhomogeneity of definitions and quantification of pulsatile flow between different studies makes comparisons challenging, and high-quality randomized clinical trials are needed to provide additional evidence.

Acid–base balance

Acid–base imbalance after CPB is common, and hyperlactatemia can occur even in the absence of inadequate tissue perfusion, which might be attributed to the impact of hypothermia on metabolism [175], moreover, the use of catecholamines during surgery leads to increased lactate levels [176]. One study suggested that postoperative hyperlactatemia is associated with poor outcomes and mortality, and 0.75 mmol/L is an appropriate cutoff [177].

Early findings suggest that, given the hypothermic environment intraoperatively, an alpha-stat (temperature-uncorrected blood gas management) is associated with less postoperative cerebral dysfunction than a pH-stat (temperature-corrected blood gas management) [178,179]. A review recommended that the best management of acid–base therapy is dependent upon patient age, with the use of a pH-stat in pediatric patients and an alpha-stat in adult patients [180]. The results of a clinical trial also confirmed that the pH-stat is superior in the pediatric population [181].

However, these conclusions require further validation in larger cohorts. Additionally, considering the crucial role of the kidneys in maintaining acid–base balance, it is essential to explore outcomes related to renal function.

Goal-directed haemodynamic therapy

Given the limited tolerance of organs to ischemic and hypoxic conditions, the concept of intraoperative and perioperative haemodynamic management has been proposed and extensively studied. Goal-directed haemodynamic therapy (GDT) is a strategy based on increasing cardiac output by using fluids and medicine [182] and has been shown to reduce postoperative complications and length of ICU stay in cardiac surgical patients with CPB [183], however, no difference in renal outcome was detected. Similar results were demonstrated in a meta-analysis and systematic review [184]. Recently, a small prospective study demonstrated that GDT fails to reduce the incidence of AKI, but the level of cystatin-C was lower in the GDT group than in the control group [185]. In brief, there is a lack of kidney evidence, yet large multicenter studies are desirable to demonstrate the presented concept in daily clinical practice.

Remote ischemic preconditioning

Remote ischemic preconditioning (RIPC) is a technique in which brief episodes of ischemic protection or 'preconditioning' are applied to distant tissues or organs to endure a subsequent episode of sustained ischemia; this technique was first proposed for use in dog coronary artery experiments [186], after which the nephroprotective effect was later confirmed [187].

The success of animal experiments has led to the development of clinical research, but progress has not been smooth. There has been ongoing debate regarding the renoprotective effects of RIPC in cardiac surgery with CPB [188,189]. In large cohorts, RIPC did not significantly improve renal outcomes, including postoperative AKI occurrence and renal indices (serum creatinine, urea nitrogen, and cystatin-C) [190]. Moreover, after adjusting for baseline creatinine, RIPC reduced the incidence of AKI after cardiac surgery in a small RCT of congenital heart defect children [191]. A high-quality meta-analysis indicated that RIPC does not significantly reduce the incidence of ischemia–reperfusion AKI [192]. This finding suggested that in CPB surgeries, where ischemia is the primary pathogenic mechanism, the renal benefits of RIPC require further investigation.

There are several potential reasons for these results. Apart from the variations in the RIPC protocols and the definitions of renal outcomes, high blood sugar levels appear to negate the renoprotective effects of RIPC [193]. Additionally, animal studies have indicated that the method of anesthesia can also impact patient outcomes [194]. Recent studies have confirmed the crucial role of exosomes in RIPC, potentially contributing to the protective mechanisms against ischemic damage in organs [195,196]. These findings position exosomes as promising candidates for therapeutic strategies.

Additionally, in light of the growing focus on the precursory stages of AKI, a range of new biomarkers, which can detect renal damage earlier than creatinine, have emerged [16]. This development necessitates additional research to more accurately determine the early renal effects of this technology.

Temperature

The role of temperature in CPB has always been controversial, hypothermia results in low oxygen consumption and metabolic levels but leads to cytoskeletal changes and stress protein generation at the same time [197] and might prompt renal vasoconstriction [198].

Therapeutic hypothermia (TH) is a strategy aimed at preventing ischemic organ damage, and earlier studies have indicated that perfusion temperature (28 °C, 32 °C, and 37 °C) does not affect perioperative renal function [199]. According to a meta-analysis, TH failed to prevent the occurrence of AKI following CPB surgery [200], although variation or absence of the AKI definition was found among individual trials.

Hyperthermic perfusion is deemed to be correlated with AKI and is recommended for avoiding arterial outlet temperatures greater than 37 °C [201]. Recently, in a retrospective study of 5672 patients who underwent CPB surgery,

investigators found that mild hypothermia was associated with improved survival but lacked kidney outcomes; they also highlighted the importance of cooling and the rewarming rate [202].

In conclusion, based on the limited evidence available, mild hypothermia seems to have some protective effects on renal function during CPB. However, most current trials have not focused primarily on renal endpoints, have small sample sizes, or lack a uniform definition of AKI. Therefore, further research is needed to determine the optimal temperature and rate of achieving this goal.

Medical therapy

Exosomes

Exosomes (Exos) and microvesicles (MVs) are membrane vesicles of endosomal and plasma membrane in the extracellular environment and represent an important pattern of intercellular communication [203]. The autophagy regulator miR-590-3p, which plays a pivotal role in the repair of renal tubular cell damage, is transferred by plasma-derived Exos and is increased in young AKI patients after cardiac surgery with CPB [204].

Nevertheless, studies have shown that these microparticles could be released by erythrocytes under stress or long-term storage conditions and decrease NO bioavailability, which might underlie the pathogenesis of organ damage during hemolysis and blood transfusion [205]. Recently, research on patients undergoing CPB first confirmed the early increase in RBC-derived Exos following aortic cross-clamp release; additionally, animal experimental models have validated the ability of Exos to target the kidneys and mediate AKI [206]. However, the present study did not establish a direct correlation between elevated Exos and patient renal injury or significant differences in MVs. Future studies might broaden the scope of these methods to include microparticles from various cellular origins and extend their analyses to multiple time points during and after CPB, as the effects of CPB on organs are known to persist for up to three days postoperatively [207], not just immediately following the procedure.

In addition, these studies also serve as a reminder to exercise caution in considering exosomes as therapeutic agents or carriers, as the effects of these substances are not fully understood in all contexts [208].

Renal vasodilation

Pharmaceuticals are another tactic; as a selective dopamine-1 receptor agonist, a low dose of fenoldopam can dilate the renal vasculature without altering arterial pressure [209] and has shown a better ability to enhance RBF during CPB in a cardiac-renal perfusion model [210]. Another vasodilator, levosimendan, also displayed favorable results in alleviating hypoperfusion in a clinical trial, in addition to increasing the glomerular filtration rate (GFR), which is not amenable to dopamine. An experiment in which sheep were subjected to a low dose demonstrated that intraoperative metaraminol could increase renal oxygen and mean arterial pressure [39].

Considering the complexity of the operation and ethics, most related studies are limited by the use of models or animals and lack direct evidence for decreasing the incidence of AKI.

Nitric oxide

NO is a classical vasodilator; however, considering the different types of nitric oxide synthase (NOS), the effects on the kidney can be totally different [211]. Endothelial NOS (eNOS) primarily affects medullary perfusion and has a protective effect on the kidney [212], while inducible NOS (iNOS) participates in vascular dysfunction and tissue damage by inhibiting eNOS-derived NO and generating peroxynitrite [213,214]. In addition, NO plays an essential role in mediating electrolyte metabolism by inhibiting the activity of the Na^+-K^+-$2Cl^-$ cotransporter and reducing Na^+/H^+ exchange [215], and the NO/O2 ratio can act as a regulator of mitochondrial respiration to change the level of RVO2 [212]. A recent study suggested that NO might relieve oxidative reactions by transforming oxyhemoglobin [111, 216] and may act as an anti-inflammatory and antithrombotic mediator [217].

Given the essential role of NO, a clinical study of prolonged CPB (over 90 min) among Chinese patients indicated that administering NO (80 parts per million [ppm]) intraoperatively and on the first postoperative day significantly reduced the incidence of AKI incidence and the incidence of AKI-related AKI [218]. A similar outcome was observed in another trial in which a lower NO dose (40 ppm) was used [219]; however, recently, animal investigations have also indicated the positive function of NO in preventing AKI post CPB and provided histologic evidence [220]. However, a retrospective cohort study of children revealed that 20 ppm of NO during the CPB circuit fails to diminish the incidence of AKI [221], and treatment with NO might not be suitable for patients with acute respiratory distress syndrome [222].

In brief, the optimal curing dose and timing of NO administration for preventing AKI after CPB still need to be verified, and an explicit understanding of the protective mechanism in the kidney is imperative.

Regulating the inflammatory response

As mentioned above, immunoparalysis after CPB has been widely recognized, and investigations have indicated that increased catabolism of arginine might be a potential mechanism [223]. Additionally, exogenous supplementation with L-arginine successfully rehabilitates the proliferative ability of T cells *in vitro* [75] and is likely to lead to the development of an economical and effective hedge to reduce postoperative infection risk and the necessity of implementing nephrotoxic antibiotics.

Rat experiments demonstrated that infusion of IL-10-transformed macrophages could promote the release and function of neutrophil gelatinase-associated lipocalin (NGAL; also known as siderocalin) to mitigate ischemic kidney impairment [224], and the use of EVs provides precise and stable nanotherapeutics to transport IL-10 [225]; however, the clinical practice and effectiveness of these agents during extracorporeal circulation remain to be confirmed. Surprisingly, in addition to medical treatment, in a small study, sustained mechanical ventilation during the CPB extracorporeal period diminished the postoperative concentrations of CCL2 and CCL4, chemokines that induce a systemic inflammatory response [226], but the underlying mechanism still remains to be determined.

Recently, a study of 19 patients demonstrated that the levels of subfractionin, maresin-1, asprosin, and alamandine change significantly after CPB, and these hormones are associated with the elimination of inflammation and oxidative stress [67]. Moreover, persistent elevation of nuclear and mitochondrial cell-free DNA levels is related to systemic inflammation in pediatric cardiac surgery with CPB [227] and is valuable for future treatment [228].

A haemoadsorption (HA) device is designed to remove molecules from the extracorporeal blood circulation and terminate activation of the inflammatory response; disappointingly, the HA apparatus fails to decrease the cytokine level or complication incidence, and insufficient treatment time restricted by CPB duration might be responsible [229,230]; however, the safety and feasibility of this device have been confirmed.

Blood purification techniques have been extensively studied for toxin clearance, and subzero-balance ultrafiltration during CPB has recently been successful at extracting multiple immunomodulators and inflammatory mediators based on molecular mass [66], which offers solid testimony and reference for future research.

Colchicine is a traditional anti-inflammatory medicine, and a low dosage of colchicine perioperatively (0.5 mg once daily) reduces inflammatory indicators and has cardioprotective effects after CPB [231]. Recently, the gut microbiota was found to be involved in intestinal vulnerability, and Lactobacillus murinus might ameliorate intestinal ischemia–reperfusion (I/R) injury through TLR2 to increase the release of IL-10 from macrophages [232]. Considering the common pathogenic role of I/R and inflammatory activation in organ damage, these studies provide new insights into the prevention of CPB-related AKI.

Antioxidative stress

Although the pathogenic role of oxidative stress has been confirmed in AKI, antioxidant therapy is not effective in patients undergoing cardiac surgery with CPB [233]. The antioxidant vitamin E demonstrated an adequate curative effect in a large cohort of patients with hypercholesterolemia [234]; nevertheless, given the time of medicament onset and the urgency of cardiac surgery, this treatment seems unavailable.

Haptoglobin (Hp) is a major plasma-binding protein for free Hb. In the early century, the administration of Hp was found to mitigate renal loss after CPB surgery by decreasing free Hb [235], and glucocorticoids seemed to increase the level of Hp and prevent kidney oxidant injury in animals [236].

A recent study reaffirmed elevated cell-free plasma Hb levels in CPB-associated AKI [206, 216], which is likely to aggravate the consumption of NO [110]. Additionally, free Hb contributes to the oxidative stress response [79], and Hp-bound Hb also promotes peroxidase activation [237]. In subsequent animal experiments, acetaminophen seemed to eliminate the oxidant induced by haemoglobin [238]. Surprisingly, exposure to hyperoxaemia might augment oxidative damage [239], but avoidance of supranormal arterial blood oxygen tensions during extracorporeal circulation failed to decrease the incidence of AKI in a multicenter clinical trial [240].

Intravenous sodium bicarbonate injection was first demonstrated to prevent CPB-associated AKI [241], partially due to the function of urine alkalinization in attenuating oxygen radical production and the level of free ferric ions [85]; however, the controversy has persisted. Some researchers suggest that bicarbonate might be appropriate only for particular populations. Patients with a low risk of AKI are likely to benefit from this treatment and even have a lower mortality risk [242–244]. On the other hand, metabolic acidosis is common after extracorporeal circulation, as the accumulation of lactate and bicarbonate, which are essential components of the physical fluid alkalinization system, is worth investigating intensively.

In the past few years, animal experiments have made great progress. Ghrelin improved the glutathione content of mice during CPB and mitigated organ failure [245]. Baicalin has been shown to ameliorate renal injury in an optimized CPB mouse model and suppress the expression of iNOS [246]. The calcium channel blocker diltiazem can increase superoxide dismutase (SOD) (a natural antioxidant enzyme) activity and alleviate lipid peroxidation to protect the kidney, and these effects are enhanced when diltiazem is combined with tadalafil [247]; however, clamping of the renal artery cannot represent the clinical procedure used for CPB completely.

Similarly, macrophage migration inhibitory factor (MIF) is considered to be a protective factor in the early phase of myocardial I/R injury [248] and is currently found to be decreased in cardiac surgery patients with postoperative AKI. Researchers subsequently demonstrated that the administration of MIF could augment cytoprotective capacity by restoring intracellular GSH and inhibiting peroxidation in the kidney [249]; however, although the results of animal experiments are encouraging, considering the ability of MIF to activate inflammation in the prolonged period [248], the long-term effects of MIF in the kidney also require clarification.

In addition to medicinal strategies, metal nanoparticles and carbon-based nanomaterials with redox properties have been widely studied for their potential use in curing I/R

injury [250]. Currently, low-level light therapy during peripheral circulation can erase the activation and damage of extravasated red blood cells in pigs and promote resistance to oxidative stress [251].

Increased renal functional reserve

The renal functional reserve (RFR), the change in the glomerular filtration rate (GFR) from baseline to a peak value, represents the capacity of the kidney to respond to physiologic or pathologic stimuli and can be induced clinically by a protein load [252,253].

Within the setting of CPB, a preoperative decrease in the RFR is a high risk factor for AKI [254]. Furthermore, in postoperative AKI patients, a marked decrease in the RFR is observed after three and twelve months, respectively, and the ability of urinary AKI biomarkers to predict a decrease in the RFR in nonclinical AKI patients has also been confirmed [255].

Clinical randomized trials indicate that a preoperative high-protein oral load is associated with a preserved eGFR at 3 and 12 months after cardiac surgery with CPB [256], and intravenous amino acid therapy also reduces the duration of AKI [257], despite the failure to reduce the incidence of AKI.

These observations suggest that a recruitable RFR possesses profound physiological and therapeutic importance among individuals undergoing CPB; however, there must be a parallel reduction in the RFR due to its progressive utilization [252]. The 'premature depletion' of kidney reserves requires further consideration in terms of safety and long-term clinical benefits. In addition, for the routine clinical application of RFR, establishing a standardized and dependable measurement technique for RFR is currently a top priority.

Nanotechnology

Numerous drugs have shown promise in preventing and treating AKI, but their applications are greatly impeded by their physicochemical characteristics, such as hydrophobicity, stability, bioavailability, and inadequate renal concentration. The emergence of nanomaterials, however, represents a turning point. NPs, composed of natural polymers, polymers, organic substances, or lipids, constitute a novel drug delivery system [258]. Influenced by the glomerular filtration barrier, controlling the size of nanomaterials (diameters of 100 nm) enables targeted accumulation of drugs in damaged renal tubules [259]. In addition to glomerular filtration, mesoscale nanoparticles (with diameters of 350–400 nm) have been demonstrated to possess selective renal targeting capabilities, which are likely achieved through endocytosis by endothelial cells surrounding renal tubular capillaries [260,261].

Moreover, some inorganic nanoparticles, including ceria, carbon nanodot, copper, gold, and molybdenum, can scavenge ROS. Ceria nanoparticles effectively reduce renal tubule necrosis by decreasing oxidative stress and inflammatory responses in a mouse model of sepsis-induced AKI [262], and molybdenum-based polyoxometalate nanoclusters prevent ROS-induced AKI [263].

The results from these animal studies are inspiring, but in the unique environment of CPB, the stability of nanocomposites needs to be reevaluated to withstand the influences of surgery, extracorporeal conditions, low temperatures, and turbulence, as well as the clearance effects of intraoperative dialysis filtration. Currently, there is a lack of corresponding research. Nanomaterials have also been explored as a choice for CPB circuit tubing. Disappointingly, although surface-bound carbon nanotubes are considered to alleviate blood-surface interactions to prevent platelet activation and modulate blood biocompatibility [264], *in vivo* animal experiments first demonstrated that surface-bound multiwalled carbon nanotubes cause devastating thrombosis during extracorporeal circulation [265].

Conclusion

AKI is a general and critical complication of cardiac surgery, and CPB plays a distinctive role in the pathogenesis of AKI. The series of physiological and pathological changes resulting from CPB-specific manipulations and equipment mainly involves hypoperfusion and hypoxia, inflammation, oxidative stress, coagulation and hemolysis, and endothelial damage. Given the consideration of the causative factors, CPB-associated AKI is theoretically preventable, and critical judgment of the benefits to the surgical population, optimized CPB, and necessary medical intervention are all potentially effective strategies. Although clinical evidence is still insufficient and controversial, the future is promising, and additional studies are urgently needed to verify clinical efficacy.

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